Cyclical Ischaemic Preconditioning Modulates the Adaptive Immune Response in Human Limb Ischaemia-Reperfusion Injury

Sullivan PJ, Sweeney KJ, Hirpara KM, et al. Brit J Surg 2009;96:381-390.

Conclusion: Limb reperfusion injury can be modulated by ischemic preconditioning.

Summary: Ischemic preconditioning of reperfused tissues occurs when tissues are exposed for a short period to ischemia and then followed by a recovery period free of the stimulus. This seems to render them more resistant to subsequent ischemia-reperfusion injury. Mechanisms of ischemic preconditioning are poorly understood. It is known that ischemia and ischemic preconditioning can have effects on both innate and adaptive immune systems. In this study, the authors hypothesize modulation of T-cell function may be a mechanism by which ischemic preconditioning confers protection against reperfusion injury.

The authors evaluated systemic T-cell populations for their function and activation in patients undergoing anterior cruciate ligament repair using a tourniquet. Patients were included if they had no other comorbidities, took no regular medication, and were otherwise healthy. There were 25 patients randomized to preconditioning or control. In patients undergoing ischemic preconditioning during anterior cruciate repair, the leg operated on was elevated and exsanguinated; then, the tourniquet was inflated to at least 100 mm Hg greater than systolic blood pressure. Inflation was maintained for 5 minutes and then released for 5 minutes. Two further cycles of preconditioning were performed in the treated patients. In control patients, a tourniquet was applied but was not inflated before the actual inflation of the tourniquet for the operation. Systemic levels of interleukin (IL) 4 and interferon-γ and surface expression of CD45ro/ra and CD62L and CD95 were measured. T cells were examined systemically and in simulated serum co-culture to determine CD4/CD8 and Th1/Th2 shifts through intercellular cytokine production.

Without ischemic preconditioning, CD4 and CD45ro cell numbers increased after reperfusion injury. CD8 cells expressing CD45ro and CD95 increased with ischemic preconditioning. Preconditioning serum in co-culture attenuated increases in CD4 and decreases in CD8 cell numbers. After reperfusion injury, IL-2 levels were lower after ischemic preconditioning. Co-culture with post-reperfusion injury serum increased proinflammatory intercellular cytokine production.

Comment: The data indicate ischemic preconditioning prevents lymphocyte-directed immune dysfunction through activation and proinflammatory cytokine production by CD4 cells, at the same time preventing CD4/CD8 cellular derangement. The systemic cellular and cytokine changes observed lend support to a possible role for circulating lymphocytes in remote ischemic preconditioning. (Remote ischemic preconditioning is where ischemia is administered to tissues that will not themselves undergo reperfusion injury.) Patients likely to have a marked reperfusion injury may be considered for remote ischemic preconditioning while their urgent ischemic condition is being treated.

Effect of Dipyridamole Plus Aspirin on Hemodialysis Graft Patency

Dixon BS, Beck GJ, Vazquez MA, et al. N Engl J Med 2009;360:2191-201.

Conclusion: Use of the combination of dipyridamole plus aspirin reduces risk of stenosis and improves duration of primary unassisted patency of newly created arteriovenous grafts.

Summary: Arteriovenous grafts remain a common source for dialysis access. Although it is generally possible to restore patency to arteriovenous grafts after thrombosis, such procedures are costly. The annual cost of procedures related to vascular access is estimated to exceed $1 billion in the United States (US Renal Data System. 2007 Annual data report: atlas of end-stage renal disease in the United States. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, 2007). It is postulated that because dipyridamole acts by inhibiting the proliferation of vascular smooth muscle cells and that its use in treatment of patients with newly created hemodialysis access may improve patency of the dialysis access graft. The authors therefore performed a randomized, double-blind, placebo-controlled trial to determine whether extended-release dipyridamole plus aspirin inhibited stenosis of vascular access and prolonged primary unassisted patency of newly created dialysis access grafts.

Patients were randomized to receive dipyridamole at a dose of 200 mg and aspirin at a dose of 25 mg twice daily, or placebo, after placement of a new arteriovenous dialysis access graft. The primary outcome was loss of primary unassisted patency of the access graft. Secondary outcomes included cumulative graft failure and death.

Thirteen centers in the United States participated in the study, and 649 patients were randomly assigned to receive dipyridamole plus aspirin (321 patients) or placebo (328 patients). The study extended for 4.5 years, with an additional 6 months of follow-up. Blood flow rates at access sites were measured each month after the patient started on hemodialysis. Measurements were done using ultrasound-indicated dilution techniques.

Baseline characteristics of the two study groups were similar, as were graft blood flow rates at the time of baseline measurement. Of the grafts placed, 94% were expanded polytetrafluoroethylene, and 5% were made from some other synthetic materials. Twenty-nine percent of the grafts were forearm grafts and 44% were in the upper arm, with 6% in the leg. The rate of adherence to the study medication regimen was 83% in both groups.

At 1 year, primary unassisted patency was 23% (95% confidence interval [CI], 18%-28%) in the placebo group and 28% (95% CI, 23%-35%) in the dipyridamole-aspirin group. Adjusting for prespecified factors, the hazard ratio (HR) for loss of primary unassisted graft patency in the dipyridamole plus aspirin group compared with the placebo group was 0.82 (95% CI, 0.68-0.98; $P = .03$). This provided a relative reduction in the rate of loss of primary unassisted graft patency of 18%. The HR for loss of primary unassisted graft patency in the dipyridamole-aspirin group compared with the placebo group was 0.76 (95% CI, 0.60-0.96; $P = .02$) among patients not receiving aspirin at baseline and 0.92 (95% CI, 0.68-1.24; $P = .57$) among those receiving aspirin at baseline. There was an overall 28% reduction in rate of stenosis of >50% from treatment with dipyridamole plus aspirin (HR, 0.72; 95% CI, 0.57-0.90; $P = .005$). Mean duration of primary patency was 5.8 months (95% CI, 4.3-7.1) in the extended-release dipyridamole-aspirin group and 4.3 months (95% CI, 3.6-5.4) in the placebo group.

Comment: The data indicate that the combination of extended release dipyridamole plus aspirin in patients who had not previously received aspirin therapy had a statistically significant effect on extending primary patency of hemodialysis access grafts. The effect was modest and not clinically important. The aspirin and dipyridamole combination delayed by 6 weeks the median time to loss of primary patency in patients with newly created arteriovenous grafts. Put another way, the drug combination provides a reduction in the number of patients with primary graft failure by one patient for every 20 patients treated for 1 year. Because treatment with dipyridamole plus aspirin can cost between $5000 and $2200 per year, it is unclear if this therapy is cost-effective. The importance of this study is that it indicates that pharmacologic therapy targeting intimal hyperplasia potentially can improve the patency of dialysis access grafts. However, a better, more robust, effect will be needed to change practice.

Increased Oxidant Activity Mediates Vascular Dysfunction in Vibration Injury

Hughes JM, Wirth O, Krajnak K, et al. J Pharmacol Exp Ther 2009;328: 223-30.

Conclusion: Vibration causes vascular dysfunction in digital arteries by increasing levels of reactive oxygen species (ROS).

Summary: There are almost 1.5 million workers in the United States exposed to hand-transmitted vibration. Extrapolated from epidemiologic studies, almost half of these workers will eventually present with some manifestation of hand-arm vibration syndrome (HAVS). Anatomically, the predominant vascular disorder is increased constriction of digital arteries. HAVS can be associated with smooth muscle hypertrophy and medial thickening, with overall increases in wall-lumen ratios and a subsequent reduction in internal diameters of the digital arteries. Little is known about the onset and progression of this disease at the cellular and molecular level. The goal of the current study was to examine the effects of vibration on functional responses of digital arteries and to try and elicit the underlying mechanisms of vibration injury. The authors used a rat model of vibration injury and in preliminary work characterized the response of the digital vessels in paws to vibration. They used control and vibrating paws and then examined the digital arteries ex vivo to determine vascular responses associated with acute vibration injury.

Rat paws were exposed to a vibrating platform (4 hours, 125 Hz, constant acceleration of 49 m/s^2). Digital artery function was assessed in vitro with a myograph system. Experiments indicated that constriction to phenylephrine or 5-hydroxytryptamine was reduced in digital arteries from vibrated paws. After endothelium denudation, the agonist no longer impaired constriction in vibrated arteries. If N-nitro-L-arginine methyl ester (L-NAME) was used to inhibit nitric oxide synthase (NOS), there was increased constriction in vibrated but not control arteries to phenylephrine or 5-hydroxytryptamine. Nitric oxide activity was reduced in vibrated compared with control arteries. There were increased endogenous levels of ROS in vibrated compared with control arteries. Increased ROS levels were abolished by L-NAME. Catalase, which degrades extracellular hydrogen peroxide, increased constriction to phenylephrine or 5-hydroxytryptamine in vibrated but not control arteries. It abolished vibration-induced depression and constrictor responses.

Comment: The study suggests that an uncoupling of endothelial NOS in response to acute vibration increases ROS levels and subsequent vascular dysfunction in vibrated digital arteries. The clinical implication is that therapeutic strategies to augment nitric oxide activity or inhibit ROS may be beneficial in patients exposed to vibrating tools.

No-Show Rates in the Vascular Laboratory: Analysis and Possible Solutions

Satiani B, Miller S, Patel D. J Vasc Interv Radiol 2009;20:87-91.

Conclusions: No-show rates for the vascular laboratory present a significant opportunity for cost savings and improvement in efficiency. No-show rates do not appear to be reduced by automated reminder systems.